

REMARKS/ARGUMENTS

Upon entry of this amendment claims 71-74, 76-77, and 79-82 will be pending and under examination. In this amendment claims 25, 75 and 78 have been cancelled and new claims 79-82 have been added. Cancellation of claims is without prejudice to future prosecution of the cancelled subject matter.

This amendment is in response to an Office Action mailed January 18, 2007, which is sometimes referred to herein as the "2007 Office Action." The 2007 Office Action refers at various points to an earlier Office Action, mailed April 21, 2005. For convenience, the Office Action mailed April 21, 2005, is sometimes referred to herein as the "2005 Office Action."

I. Summary of Rejections

In Paragraph 4 of the Office Action, claims 25 and 74-78 remain rejected under 35 USC 112, first paragraph (Written description) for reasons set forth in Section 9, pages 9-12 of the Office Action mailed April 21, 2005. *This rejection is addressed below in Section II.*

In Paragraph 5 of the Office Action, claims 25 and 71-78 remain rejected under 35 USC 112, first paragraph (Enablement) for reasons set forth in Section 8, pages 8-9 of the Office Action mailed April 21, 2005. *This rejection is addressed below in Section III.*

In Paragraph 6 of the Office Action, claims 25 and 71-78 stand rejected under the doctrine of obviousness-type double patenting. *This rejection is addressed below in Section IV.*

In Paragraph 7 of the Office Action, claim 25 is rejected under 35 USC 112, first paragraph (Written Description). *This rejection is mooted by the cancellation of claim 25.*

In Paragraph 8 of the Office Action, claim 73 is rejected under 35 USC 112, first paragraph (Written Description). *This rejection is addressed below in Section V.*

In Paragraph 9 of the Office Action, claims 71-78 are rejected under 35 USC 112, first paragraph (Written Description). *This rejection is addressed below in Section VI.*

II. Claims 25 and 74-78 Are Rejected Under 35 USC 112, First Paragraph
(Written Description)

Claims 25 and 74-78 were and remain rejected under 35 USC 112, first paragraph for "the reasons previously set forth in the paper mailed April 21, 2005, section 9, pages 9-12." Applicants respectfully note this is confusing because Section 9 of the 2005 Office Action addressed claims different from those now under examination. Thus, Applicants respectfully request the Examiner's assistance (in an interview) in clarifying the bases of the rejection, should any issues remain unresolved after entry of this amendment.

As Applicants understand it, the Office has articulated two bases for the written description rejection. First, the Office asserts the specification describes use of an immunogenic composition that contains a nucleic acid encoding the *full-length* hTERT sequence to elicit an immune response, but does not describe immunogenic compositions that contain a nucleic acid encoding a polypeptide *fragment* of SEQ. ID NO:2. Second, the Office asserts the specification does not describe immunogenic compositions that contain a nucleic acid encoding a polypeptide fragment of SEQ. ID NO:2 fused to *additional* amino acid sequences. These two bases for rejection are addressed below.

Immunogenic compositions that contain a nucleic acid encoding a polypeptide fragment of SEQ. ID NO:2 are described

The Office asserts there is insufficient description of immunogenic compositions that contain a nucleic acid encoding a polypeptide *fragment* of SEQ. ID NO:2. Rejected claim 74, for example, reads as follows:

A composition containing a nucleic acid encoding a polypeptide *consisting of* at least 10 contiguous amino acids of SEQ. ID NO:2, wherein the composition elicits an adaptive immune response against hTERT (SEQ. ID NO:2) when administered to a subject.

The Office has acknowledged the specification discloses polynucleotides encoding the full-length amino acid sequence of hTERT *and* discloses polynucleotides encoding fragments of

hTRT.¹ The Office also acknowledges "one would *immediately envision* that the full length sequence will elicit an adaptive immune response against SEQ ID NO:2 . . ." (emphasis added). However, the Office asserts "the same cannot be said . . . for undefined fragments encoded by the claimed nucleic acids wherein no correlation has been made between structure and specific function of eliciting an adaptive immune response specific for SEQ ID NO:2."² Applicants respectfully disagree with this characterization. First, the hTRT fragments disclosed by the inventors are *not* "undefined." Rather, the polypeptides are defined by SEQ ID NO:2. Provided with SEQ ID NO:2 and the teachings of the specification, one of skill would *immediately envision* the hTRT fragments. Second, there is a *clear* correlation between the structure of the fragments and their function. The encoded polypeptides include hTRT sequence (structure) and elicit an immune response to the hTRT sequence (an activity correlated with the defined structure). If, as the Office correctly acknowledges, one of skill would *immediately envision* that the full length sequence will elicit an adaptive immune response against SEQ ID NO:2 Applicants believe it beyond dispute that one of skill would also envision that hTRT fragments will elicit an immune response against SEQ ID NO:2. More particularly, an hTRT fragment corresponding to a particular region of the hTRT protein (i.e., a particular amino acid sequence) will elicit an immune response to epitopes located in the particular region.

The Office states ". . . one cannot envision the structure of the claimed nucleic acids in the compositions by the combination of structure and function because the specification provides no teach[ing] drawn to . . . which encoded fragments are immunogenic . . ."³ Applicants respectfully disagree. The Office has argued previously "all molecules will elicit an

¹See, e.g., 2005 Office Action at page 9, lines 23-25.

² 2007 Office Action at p. 4, lines 1-9: "The written description in this case . . . sets forth nucleic acid encoding SEQ ID NO:2, SEQ ID NO:1 and fragments thereof . . ." (Omitting the central ellipsis the full citation reads "The written description in this case only sets forth nucleic acid encoding SEQ ID NO:2, SEQ ID NO:1 and fragments thereof . . .").

³ 2007 Office Page 3, lines 7-19. Omitting the central ellipsis, the citation reads ". . . one cannot envision the structure of the claimed nucleic acids in the compositions by the combination of structure and function because the specification provides no teach[ing] drawn to the structure of nucleic acids encoding the claimed proteins which consist of or comprise immunogenic fragments, that is which encoded fragments are immunogenic . . .". Also see Page 5, lines 1-5, ". . . the genus is drawn to a whole multitude of nucleic acids encoding fragments wherein the specification does not provide sufficient information drawn to the structure that functions to elicit an adaptive immune response against SEQ ID NO:2 . . ."

immune response [to themselves] under appropriate circumstances."⁴ Applicants submit that hTERT fragments are molecules that will elicit an immune response to themselves and to corresponding epitopes on full-length hTERT. This is understood by biologists with undergraduate level training and would certainly have been recognized by those of ordinary skill in the biomedical arts. In addition, the specification provides working examples showing induction of an immune response by inoculating non-human animals with short polypeptide comprising hTERT sequence (see, e.g., Example 6)⁵ as well as production of fusion proteins containing hTERT fragments for use as immunogens (see, e.g., Example 8)⁶.

Immunogenic compositions that comprise a nucleic acid encoding a polypeptide fragment of SEQ. ID NO:2 are described

The Office also asserted the specification does not describe immunogenic compositions that contain a nucleic acid encoding a polypeptide fragment of SEQ. ID NO:2 fused to an additional amino acid sequence. This rejection appears to have been directed to Claim 25,⁷ and is thus mooted by the cancellation of the claim.

Applicants note that pending claims with open language encompass hTERT fragments with additional flanking sequences.⁸ If this basis of rejection is believed relevant to any current claim, Applicants point out that the current claims clearly recite that the composition elicits an immune response against SEQ ID NO:2, rather than against any flanking sequence. Thus, the concerns previously articulated by the Office that "given the undefined and apparently unlimited nature of the claimed polynucleotides, it is apparent that the immunogenic functions of the . . . polynucleotides are both unknown and highly varied *given that the claims are not limited to an*

⁴ 2005 Office Action, page 10, first full paragraph.

⁵ Pages 176-177. Page and line numbers refer to the specification as filed.

⁶ E.g., pages 160-163.

⁷ See page 5 of 2007 Office Action.

⁸ For example, claim 76 reads: A composition containing a nucleic acid encoding a polypeptide that comprises at least 10 contiguous amino acids of SEQ. ID NO:2, wherein the composition elicits an adaptive immune response against hTERT (SEQ. ID NO:2) when administered to a subject.

*immunogenic composition that . . . stimulated an immune response against a polynucleotide encoding SEQ ID NO:2*⁹ are not relevant to the current claims.

Conclusion

Section 112 requires that the applicant has conveyed to those of skill in the art that he or she was in possession of the claimed invention at the time of filing. The identification by the inventors of human telomerase reverse transcriptase (hTERT) was a scientific breakthrough and one of the seminal achievements of the late 1990s. In a lengthy and detailed specification Applicants disclosed the use of hTERT polypeptides and polynucleotides to, *inter alia*, elicit an immune response. Applicants submit one of skill reading the specification would clearly recognize the inventors' "possession" of the claimed subject matter. The medical community has recognized Applicants' contribution, and applied and followed Applicants teachings. For example, as noted by Carpenter et al.:¹⁰

The progression from the cloning of human telomerase reverse transcriptase (hTERT) in 1997 to the first clinical trials of hTERT as an antitumour immunotherapy target has been swift. hTERT is overexpressed in the vast majority of human cancers yet has limited expression in normal adult tissue. It plays a critical role in oncogenesis and may be expressed by cancer stem cells. However, despite being a self antigen, hTERT is immunogenic both in vitro and in vivo. Several Phase I studies of hTERT immunotherapy have been completed in patients with breast, prostate, lung and other cancers, and clinical and immunological results are encouraging.

Applicants respectfully request this rejection be withdrawn.

III. Rejection of Claims 25 and 71-78 Under 35 USC 112, First Paragraph (Enablement)

Claim 25 and 71-78 were and remain rejected under 35 USC 112, first paragraph (Enablement) for reasons set forth in Section 8, pages 8-9 of the Office Action mailed April 21, 2005.

⁹ See 2005 Office Action, paragraph spanning pages 11-12. Applicants' comments do not indicate acquiescence to the position of the 2005 Office Action.

The rejection in Section 8 of the prior Office Action was premised on a misunderstanding of the claims. The Office stated ". . . there is no teaching of how to use an immunogenic composition that produces antibodies or cytotoxic T-cells that specifically target the nucleic acids encoding a protein or fragment thereof." It appears from this that the Office believed that the immune response was directed against the nucleic acid. However, the immune response is directed against the polypeptide encoded by the nucleic acid. This is basic to the process of eliciting an immune response using "naked DNA" (as described in the specification). Applicants have previously explained (see response filed November 10, 2005 at page 11) that the immune response was not against a nucleic acid. However, because Applicants previously addressed the issue in the context of a rejection under 35 USC 112, second paragraph, it appears to have not been considered by the Office to be responsive to the 35 USC 112, first paragraph, rejection.

The Office also wondered how a DNA in the nucleus of a cell would be targeted. As noted, the immune response is not directed against the DNA. Accordingly, this rejection should be withdrawn.

IV. Obviousness-Type Double Patenting Rejection

In Paragraph 6 of the Office Action, claims 25 and 71-78 stand rejected under the doctrine of obviousness-type double patenting as previously set forth in the Office Action mailed April 21, 2005, sections 12 and 13.¹¹ The Office stated that "Applicant states that upon indication of allowed claims, Applicant will provide terminal disclaimers . . ." This statement reflects an apparent misunderstanding by the Office.

Double patenting rejections were made citing two issued patents, Nos. 6,093,809 and 6,261,836. Applicants traversed the rejection as it applies to the '809 patent. The traversal is found in Applicants' response filed November 10, 2005 including an argument at page 12, and

¹⁰ Carpenter et al., 2006, *Expert Opinion On Biological Therapy* 6:1031-39.

¹¹ In what is clearly an editorial error, the Office Action cites 35 USC 112, first paragraph, rather than referring to double patenting.

an exhibit showing that the *Euplotes* TRT and human TRT have different sequences and that the rejection should be withdrawn. The Office is requested to revisit the amendment and contact the undersigned if she believes any issues remain.

With regard to the '836 patent, Applicants will provide a terminal disclaimer or otherwise respond to this rejection upon indication the claims are otherwise allowable.

V. Rejection of Claim 73 Under 35 USC 112, First Paragraph (Written Description)

In Paragraph 7 of the Office Action, claim 73 is rejected under 35 USC 112, first paragraph (Written Description).¹² The Office contends that a composition that contains a nucleic acid that encodes a polypeptide at least 98% identical to the full-length hTRT protein and which elicits an adaptive immune response against hTRT protein is not supported in the specification. In particular, the Office asserted lack of nexus between the sections of the specification cited in Applicants' previous amendment. Applicants respectfully traverse.

The paragraphs below explain that claim 73 has clear support in the specification. With regard to "nexus," Applicants respectfully remind the Office that, although an Applicant cannot pick and chose unrelated elements from a specification, and combine them to result in a combination never contemplated in the specification, the law permits combining related elements in a specification to craft a particular claim. In the present case, the entire specification is focused on compositions and uses related to a particular protein, hTRT. One of skill in the art would find nexus between descriptions of hTRT and uses of hTRT in various parts of the specification.

The Office acknowledges that a polypeptide at least 100% identical to the full-length hTRT protein which elicits an adaptive immune response against hTRT protein is supported in the specification. The Office does not assert that there are any polypeptides at least 98% identical to the full-length hTRT protein which would not elicit an adaptive immune response

¹² For convenience, claim 73 is reproduced below:

A composition containing a nucleic acid that encodes a polypeptide comprising a sequence at least 98% identical to the 1132 residues of SEQ. ID NO:2, wherein the composition elicits an adaptive immune response against hTRT (SEQ. ID NO:2) when administered to a subject.

against hTRT protein. Indeed, it is clear that one of ordinary skill would understand that a polypeptide at least 98% identical to the full-length hTRT protein would elicit an adaptive immune response against hTRT. The sole issue, as Applicants understand it, is whether one of skill reading the specification disclosures that (1) a wide variety of hTRT polypeptides may be used to elicit an immune response, (2) some hTRT polypeptides have at least 98% identity to SEQ ID NO:2, and (3) an immune response can be elicited by administration of "naked DNA" encoding an hTRT polypeptide would not recognize that the inventors "had possession" of an hTRT polypeptide with at least 98% identity to SEQ ID NO:2 that elicits an immune response to hTRT. Applicants submit one of skill would immediately recognize such possession.

The specification discloses that "an immune response can be elicited" by administration of "naked DNA" encoding an hTRT peptide or polypeptide. See page 90, lines 13-23.

The specification also discloses that "[t]he invention provides a *wide variety* of hTRT proteins useful for, inter alia, . . . induction of an anti-TRT immune response." See page 37, lines 3-14.¹³

The specification further teaches that among the *wide variety* of hTRT proteins disclosed, some have substantial sequence identity to SEQ ID NO:2, and that "substantial sequence identity" between amino acid sequences may be sequence identity of at least 98%. See page 148, lines 3-6 (" . . . substantial sequence identity can be described as a percentage identity between two . . . polypeptide . . . sequences. Two sequences are considered substantially identical when they are . . . at least about 95% or 98% to 100% identical"),

One of skill would have no reason to believe that that "wide variety of hTRT proteins" useful for induction of an anti-TRT immune response did not include polypeptides with substantial sequence identity to the hTRT protein of SEQ ID NO:2. Rather, one of skill in the art reading the specification would have recognized that polypeptides with substantial sequence identity to the hTRT protein of SEQ ID NO:2 could be used to induce an immune response.

¹³ For the convenience of the Office and for increased clarity, excerpts of the specification presented herein have been edited and/or emphasis added to highlight relevant sections, without changing meaning. It is understood the Office will review the full text in the specification in the course of examining the claims.

In fact, at page 64, lines 20-24, the specification teaches that "[p]eptides used to induce specific antibodies typically have an amino acid sequence consisting of . . . at least 10 amino acids. Usually they will mimic or *have substantial sequence identity to all or a contiguous portion of the amino acid sequence of the protein of SEQ ID NO:2*" (italics added). This sentence clearly conveys that a polypeptide having *substantial sequence identity* to the full-length ("all . . . of the amino acid sequence of") hTRT is an immunogenic polypeptide.

One of skill would understand in view of the teachings throughout the specification that a polypeptide having substantial sequence identity to the full-length hTRT is an immunogenic polypeptide for other purposes and could be delivered in the form of naked DNA. Applicants respectfully submit Section 112 does not require that specification describe the claimed invention *ipsis verbis*. The instant specification, while lengthy and in certain respects complex, consistent with the importance of the invention, is focused on compositions and uses related to a particular protein, hTRT. Applicants respectfully submit one of skill would find "nexus" among various descriptions of hTRT and its uses, and would understand the specification to clearly convey the inventors' possession of the claimed compositions.

VII. Rejection of Claims 71-78 Under 35 USC 112, First Paragraph (Written Description)

Claims 71-78 were rejected under 35 USC 112, first paragraph (Written Description). The Office asserts that the specification teaching that "[a]n immune response can also be raised by delivery of plasmid vectors encoding the polypeptide of interest (i.e., administration of "naked DNA") is evidence that only naked DNA administered in the form of a plasmid is described. New claims 79-81 recite that the composition contains "plasmid vectors." However, as to claims 71-78 Applicants respectfully traverse the rejection.

The requirement for written description of an invention is intended to ensure that the inventor had possession of a claimed invention. The identification and cloning of human telomerase reverse transcriptase (hTRT) was a scientific breakthrough with numerous ramifications. One of ordinary skill in the art reading the instant specification would have recognized that the invention being disclosed was the hTRT gene and protein sequence and their use to elicit an immune response, not a particular vector (whether plasmid, viral, or

ballistic) for delivering an immunogenic composition. As noted in MPEP 2163.05, while a claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed may not comply with the written description requirement, this is not the case where the specification, as filed, did not describe the feature as critical.

Moreover, it is relevant that at the time the application was filed "naked DNA" was well known in the art to encompass various types of vectors and delivery vehicles. The instant specification, for example, describes administration of therapeutic *viral* vectors "in naked form." See, for example, page 57, lines 29 et seq. The instant specification teaches that nucleic acids of interest ("naked DNA") can be delivered by injection, liposomes, or other means of administration." See page 90, lines 12-23.

It is well established that description does not require *ipsis verbis* recitation of claim terms. Applicants respectfully submit that the specification as filed clearly conveyed that the inventors had possession of the use of hTERT in the form of "naked DNA" (i.e., in the form of a nucleic acid rather than a protein) to elicit an immune response, without limitation to a specific vector.

App. No. 10/044,692
Amdt. dated July 18, 2007
Response to Final Office Action dated January 18, 2007

CONCLUSION

For the reasons provided above, Applicants respectfully request that the claims now pending be examined and a Notice of Allowance issued.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-462-5330.

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Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Randolph Ted Apple', written in a cursive style.

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